

CLAIMS

We claim

1. A self-microemulsifiable base composition, comprising:
 - a) propofol; and
 - b) a nonionic surfactant.
2. The base composition of claim 1 in which the nonionic surfactant is included in the base composition in a concentration of about eight (8) parts or more of the nonionic surfactant to one (1) part of propofol.
3. The base composition of claim 1 in which the propofol contains free alpha tocopherol.
4. The base composition of claim 1 in which the nonionic surfactant contains polyethylene glycol.
5. The base composition of claim 1 in which the nonionic surfactant is PEG-660 15 hydroxystearate.
6. The base composition of claim 1 in which the base composition is anhydrous.
7. The base composition of claim 1 in which the base composition is homogeneous.
8. The base composition of claim 1 in which the base composition is optically transparent.
9. A microemulsion, comprising:
 - a) the base composition of claim 1, 2, 3, 4, 5, 6, 7, or 8; and
 - b) a carrier liquid.
10. The microemulsion of claim 9 in which the carrier liquid contains water.

11. The microemulsion of claim 9 in which the carrier liquid is isotonic to blood.
12. The microemulsion of claim 9 in which the carrier liquid is 0.9% saline in water.
13. The microemulsion of claim 9 in which the carrier liquid is 5% dextrose in water.
14. The microemulsion of claim 9 in which the carrier liquid is an isotonic solution containing crystalloid.
15. The microemulsion of claim 9 in which the carrier liquid is an isotonic solution containing colloid.
16. The microemulsion of claim 9 in which the microemulsion is thermodynamically stable.
17. The microemulsion of claim 9 in which the microemulsion is optically transparent.
18. The microemulsion of claim 9 in which the concentration of the propofol is included in the microemulsion in an amount of up to about 1% by weight of the propofol to the volume of the microemulsion.
19. The microemulsion of claim 9 in which the concentration of the propofol is included in the microemulsion in an amount of up to about 4% by weight of the propofol to the volume of the microemulsion.
20. The microemulsion of claim 9 which is intravenously injectable into a mammal.
21. A self-microemulsifiable base composition, comprising:
 - a) propofol;

- b) a nonionic surfactant;
- c) a water-immiscible solvent; and
- d) ethanol.

22. The base composition of claim 21 in which the relative concentration of the nonionic surfactant to propofol included in the base composition is about three (3) to five (5) parts surfactant to about one (1) part propofol, the relative concentration of the water-immiscible solvent to propofol is about three (3) to five (5) parts solvent to about ten (10) parts propofol, and the relative concentration of ethanol to propofol is about five (5) to six (6) parts ethanol to about ten (10) parts propofol.

23. The base composition of claim 21 in which the relative concentration of the nonionic surfactant to propofol included in the base composition is not less than about three (3) parts surfactant to about one (1) part propofol, the relative concentration of the water-immiscible solvent to propofol is about three (3) to five (5) parts solvent to about ten (10) parts propofol, and the relative concentration of ethanol to propofol is about five (5) to six (6) parts ethanol to about ten (10) parts propofol.

24. The base composition of claim 21 in which the propofol contains free alpha tocopherol.

25. The base composition of claim 21 in which the nonionic surfactant contains polyethylene glycol.

26. The base composition of claim 21 in which the nonionic surfactant is PEG-660 15 hydroxystearate.

27. The base composition of claim 21 in which the water-immiscible solvent is ethyl oleate.

28. The base composition of claim 21 in which the base composition is anhydrous.

29. The base composition of claim 21 in which the base composition is homogeneous.

30. The base composition of claim 21 in which the base composition is optically transparent.

31. A microemulsion, comprising:

a) the base composition of claim 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30;

and

b) a carrier liquid.

32. The microemulsion of claim 31 in which the carrier liquid contains water.

33. The microemulsion of claim 31 in which the carrier liquid is isotonic to blood.

34. The microemulsion of claim 31 in which the carrier liquid is 0.9% saline in water.

35. The microemulsion of claim 31 in which the carrier liquid is 5% dextrose in water.

36. The microemulsion of claim 31 in which the carrier liquid is an isotonic solution containing crystalloid.

37. The microemulsion of claim 31 in which the carrier liquid is an isotonic solution containing colloid.

38. The microemulsion of claim 31 in which the microemulsion is thermodynamically stable.

39. The microemulsion of claim 31 in which the microemulsion is optically transparent.

40. The microemulsion of claim 31 in which the concentration of the propofol is included in the microemulsion in an amount of up to about 5% by weight of the propofol to the volume of the microemulsion.

41. The microemulsion of claim 31 in which the concentration of the propofol is included in the microemulsion in an amount of up to about 10% by weight of the propofol to the volume of the microemulsion.

42. The microemulsion of claim 31 which is intravenously injectable into a mammal.

43. A method of preparing the microemulsion of claim 9 comprising the steps of:

- a) heating a predetermined amount of the nonionic surfactant to preparation temperature above its melting point; and
- b) combining the nonionic surfactant and a predetermined amount of the propofol, thereby forming the microemulsion.

44. A method of preparing the microemulsion of claim 31 comprising the steps of:

- a) heating a predetermined amount of the nonionic surfactant to preparation temperature above its melting point; and
- b) combining the nonionic surfactant, and predetermined amounts of the water-immiscible solvent, ethanol and propofol, thereby forming the microemulsion.

45. The base composition as in claim 1 in which the non-ionic surfactant has general structure $[\text{POE}(n)]_{\text{sub}m}\text{-R}'\text{-R}$; where POE is a polyoxyethylene moiety (also known as a polyethylene glycol or PEG moiety) of *-mer* number *n*, and having *m* of

these POE functional groups attached to R'; where the value of *m* is one to three; where R' is a linking moiety, particularly sorbitan, ester, amino, or ether (oxygen) functions; and where R is a hydrophobic moiety consisting of saturated or unsaturated alkyl or alkylphenyl groups.

46. The base composition as in claim 45 in which the non-ionic surfactant is selected from the group consisting of polyoxyethylene monoalkyl ethers, polyoxyethylene alkylphenols, polyethylene glycol fatty acid monoesters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, and polyoxyethylene sterols.

47. The base composition as in claim 45 in which the structure of the non-ionic surfactant is further defined by a ratio of **A**, the total number of POE *-mer* units in the surfactant (given by the product of *-mer* number *n* and total PEG chain number *m* per molecule); to **B**, the number of carbons in the hydrophobic functional group R, is between about 0.7 and 4, preferably with **A/B** being in the range from about 1 to 2.

48. The base composition as in claim 47 in which the non-ionic surfactant is selected from the group consisting of **PEG-15 monolaurate**, **PEG-20 monolaurate**, **PEG-32 monolaurate**, **PEG-48 monolaurate**, **PEG-13 monooleate**, **PEG-15 monooleate**, **PEG-20 monooleate**, **PEG-32 monooleate**, **PEG-15 monolaurate**, **PEG-20 monolaurate**, **PEG-32 monolaurate**, **PEG-48 monolaurate**, **PEG-13 monooleate**, **PEG-15 monooleate**, **PEG-20 monooleate**, **PEG-32 monooleate**, **PEG-72 monooleate**, **PEG-15 monostearate**, **PEG-660 15-hydroxystearate** (BASF Corporation's Solutol®), **PEG-23 monostearate**, **PEG-40 monostearate**, **PEG-72 monostearate**, **PEG-20 glyceryl laurate**, **PEG-30 glyceryl laurate**, **PEG-20 glyceryl stearate**, **PEG-20 glyceryl oleate**, **PEG-30**

glyceryl monooleate, **PEG**-30 glyceryl monolaurate, **PEG**-40 glyceryl monolaurate, **PEG**-20 sorbitan monooleate (polysorbate 80, Tween 80), PEG-20 sorbitan monolaurate (Tween 20), **PEG**-20 sorbitan monopalmitate (Tween 40), and PEG 20 sorbitan stearate (Tween 60), **PEG**-40 sorbitan monooleate, **PEG**-80 sorbitan monolaurate, POE-23 lauryl ether, POE-20 oleyl ether, **PEG** 30-60 nonyl phenol series (Triton N series), and **PEG** 30-55 octyl phenol series (Triton X series, particularly X-305 (POE 30) and X-405 (POE 40)).

49. The base composition as in claim 46 or 47 in which the non-ionic surfactant has general structure $[R-(POE)_{subn}]_{sub3}$ -glyceride; where POE is a polyoxyethylene moiety (also known as a polyethylene glycol or PEG moiety) of **-mer** number **n**, inserted between fatty acid acyl residues R and a glycerol residue (glyceride), which had, before polyethoxylation, been attached directly to the acyl residues as a common triglyceride.

50. The base composition as in claim 49 in which the non-ionic surfactant is a polyoxyethylated vegetable oil.

51. The base composition as in claim 49 in which the structure of the non-ionic surfactant is further defined by a ratio of **A**, the total number of POE **-mer** units in the surfactant (given by the product of **-mer** number **n** and total PEG chain number 3 per molecule); to **B**, the number of carbons in the 3 fatty acid R residues, is between about 0.5 and 3, preferably with **A/B** being in the range from about 0.6 to 1.5.

52. The base composition as in claim 51 in which the non-ionic surfactant is selected from the group consisting of **PEG**-40 palm kernel oil, **PEG**-50 hydrogenated castor oil, **PEG**-40 castor oil, **PEG**-35 castor oil (e.g., Cremaphor®-35), **PEG**-60 castor

oil, **PEG**-40 hydrogenated castor oil, **PEG**-60 hydrogenated castor oil, and **PEG**-60 corn oil.

53. The base composition as in claim 21 in which the non-ionic surfactant has general structure $[\text{POE}(n)]_{\text{subm}}\text{-R}'\text{-R}$; where POE is a polyoxyethylene moiety (also known as a polyethylene glycol or PEG moiety) of **-mer** number **n**, and having **m** of these POE functional groups attached to R'; where the value of **m** is one to three; where R' is a linking moiety, particularly sorbitan, ester, amino, or ether (oxygen) functions; and where R is a hydrophobic moiety consisting of saturated or unsaturated alkyl or alkylphenyl groups.

54. The base composition as in claim 53 in which the non-ionic surfactant is selected from the group consisting of polyoxyethylene monoalkyl ethers, polyoxyethylene alkylphenols, polyethylene glycol fatty acid monoesters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, and polyoxyethylene sterols.

55. The base composition as in claim 53 in which the structure of the non-ionic surfactant is further defined by a ratio of **A**, the total number of POE **-mer** units in the surfactant (given by the product of **-mer** number **n** and total PEG chain number **m** per molecule); to **B**, the number of carbons in the hydrophobic functional group R, is between about 0.7 and 4, preferably with **A/B** being in the range from about 1 to 2.

56. The base composition as in claim 55 in which the non-ionic surfactant is selected from the group consisting of **PEG**-15 monolaurate, **PEG**-20 monolaurate, **PEG**-32 monolaurate, **PEG**-48 monolaurate, **PEG**-13 monooleate, **PEG**-15 monooleate, **PEG**-20 monooleate, **PEG**-32 monooleate, **PEG**-15 monolaurate, **PEG**-20

monolaurate, **PEG**-32 monolaurate, **PEG**-48 monolaurate, **PEG**-13 monooleate, **PEG**-15 monooleate, **PEG**-20 monooleate, **PEG**-32 monooleate, **PEG**-72 monooleate, **PEG**-15 monostearate, **PEG**-660 15-hydroxystearate (BASF Corporation's Solutol®), **PEG**-23 monostearate, **PEG**-40 monostearate, **PEG**-72 monostearate, **PEG**-20 glyceryl laurate, **PEG**-30 glyceryl laurate, **PEG**-20 glyceryl stearate, **PEG**-20 glyceryl oleate, **PEG**-30 glyceryl monooleate, **PEG**-30 glyceryl monolaurate, **PEG**-40 glyceryl monolaurate, **PEG**-20 sorbitan monooleate (polysorbate 80, Tween 80), PEG-20 sorbitan monolaurate (Tween 20), **PEG**-20 sorbitan monopalmitate (Tween 40), and PEG 20 sorbitan stearate (Tween 60), **PEG**-40 sorbitan monooleate, **PEG**-80 sorbitan monolaurate, POE-23 lauryl ether, POE-20 oleyl ether, **PEG** 30-60 nonyl phenol series (Triton N series), and **PEG** 30-55 octyl phenol series (Triton X series, particularly X-305 (POE 30) and X-405 (POE 40)).

57. The base composition as in claim 54 or 55 in which the non-ionic surfactant has general structure $[R-(POE)_{\text{sub}n}]_{\text{sub}3}$ -glyceride; where POE is a polyoxyethylene moiety (also known as a polyethylene glycol or PEG moiety) of *-mer* number *n*, inserted between fatty acid acyl residues R and a glycerol residue (glyceride), which had, before polyethoxylation, been attached directly to the acyl residues as a common triglyceride.

58. The base composition as in claim 57 in which the non-ionic surfactant is a polyoxyethylated vegetable oil.

59. The base composition as in claim 57 in which the structure of the non-ionic surfactant is further defined by a ratio of **A**, the total number of POE *-mer* units in the surfactant (given by the product of *-mer* number *n* and total PEG chain number 3 per

molecule); to **B**, the number of carbons in the 3 fatty acid R residues, is between about 0.5 and 3, preferably with **A/B** being in the range from about 0.6 to 1.5.

60. The base composition as in claim 59 in which the non-ionic surfactant is selected from the group consisting of **PEG**-40 palm kernel oil, **PEG**-50 hydrogenated castor oil, **PEG**-40 castor oil, **PEG**-35 castor oil (e.g., Cremaphor®-35), **PEG**-60 castor oil, **PEG**-40 hydrogenated castor oil, **PEG**-60 hydrogenated castor oil, and **PEG**-60 corn oil.

61. The base composition as in claim 21 in which the water-immiscible solvent is a monoester derived from an aliphatic acid and a monoalcohol.

62. The base composition as in claim 61 in which the monoester is ethyl oleate, propylene glycol dicaprylate, isopropyl myristate, ethyl laurate, butyl oleate, oleyl acetate, oleyl propionate, octyl octanoate, octyl decanoate, or oleyl oleate.

63. The base composition as in claim 21 in which the water-immiscible solvent is a diester derived from a di-alcohol and a mono-acid.

64. The base composition as in claim 63 in which the diester is propylene glycol dilaurate, propylene glycol dioleate, propylene glycol dicaprylate or 1, 2 butane glycol dioleate.

65. The base composition as in claim 21 in which the water-immiscible solvent is a diester derived from a di-acid and a mono-alcohol.

66. The base composition as in claim 65 in which the diester is dioleyl succinate, diethyl fumarate, diethyl malate, or diethyl adipate.

67. The base composition as in claim 21 in which the water-immiscible solvent is a triester derived from an aliphatic acid and a trialcohol.

68. The base composition as in claim 67 in which the triester is a triglyceride.
69. The base composition as in claim 68 in which the triglyceride is glycerol tri-oleate or a medium chain triglyceride oil.
70. The base composition as in claim 21 in which the water-immiscible solvent is a triester derived from an aliphatic tri-carboxylic acid and a mono-alcohol.
71. The base composition as in claim 70 in which the triester is a triethyl citrate, tributyl citrate, or triethyl isocitrate.
72. The base composition as in claim 21 in which the water-immiscible solvent is selected from the group of benzoic acid esters of ethanol, n-propanol, isopropanol, and benzyl alcohol.
73. The base composition as in claim 21 in which the water-immiscible solvent is oleic acid.